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Synthesis of a Versatile (*S*)-3-(Hydroxymethyl)butane-1,2,4-triol Building Block and its Application for the Stereoselective Synthesis of N-Homoceramides

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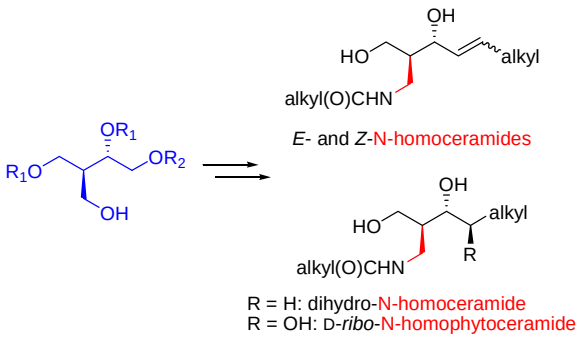
ABSTRACT



A versatile (*S*)-3-(hydroxymethyl)butane-1,2,4-triol building block has been synthesized starting from D-isoascorbic acid, a common food preservative. The key transformation in this approach was the introduction of branching through a high yield and fully regioselective epoxide opening. This flexible synthon has been elaborated to a new class of (dihydro)-N-homo(phyto)ceramides.

The development and availability of reliable and efficient methods for the construction of chiral building blocks are crucial for the synthesis of many pharmaceutical agents and complex natural products. These chiral building blocks can be derived from the chiral pool or by chemical/enzymatic means from achiral or racemic starting material.

(*S*)-3-(Hydroxymethyl)butane-1,2,4-triol is a flexible, multivalent, scaffold with defined stereochemical features which can be exploited by judicious selection of appropriate protecting groups. Some examples of the synthetic potential of this intermediate are summarized in Figure 1. Indeed, sugar derivatives (*S*,*S*)-4-(hydroxymethyl)pyrrolidine-3-ol,[1] the enantiomer of the common precursor of second-generation purine phosphorylase inhibitors[2] and oxetanocin A, a known antibacterial,

[1] (a) Tyler, P. C; Clinch, K. PCT Int. Appl. WO 2005033076, 2005. (b) Karlsson, S.; Hogberg, H.-E. *Tetrahedron: Asymmetry* **2001**, *12*, 1977-1982.

[2] (a) Kotian, P. L.; Chand, P. *Tetrahedron Lett.* **2005**, *46*, 3327-3330. (b) Makino, K.; Ichikawa, Y. *Tetrahedron Lett.* **1998**, *39*, 8245-8248. (c) Evans, G. B.; Furneaux, R. H.; Lewandowicz, A.; Schramm, V. L.; Tyler, P. C. *J. Med. Chem.* **2003**, *46*, 5271-5276.

antitumoral and antiviral natural product,[3] are readily accessible through a limited number of steps (**A**). Moreover, ceramide analogues with an inversed amide functionality (**B**) could provide useful biochemical tools for assessment of ceramide interaction with a myriad of clinically relevant enzymes. Finally, simple elaboration of the other primary alcohol (C4-OH) to the amide part (**C**) gives access to D-*threo*-PDMP homologues[4] (D-*threo*-1-phenyl-2-amino decanoyl-3-morpholinopropanol), an inhibitior of glucosyl ceramide synthase which is a potential target in the treatment of cancer.[5]

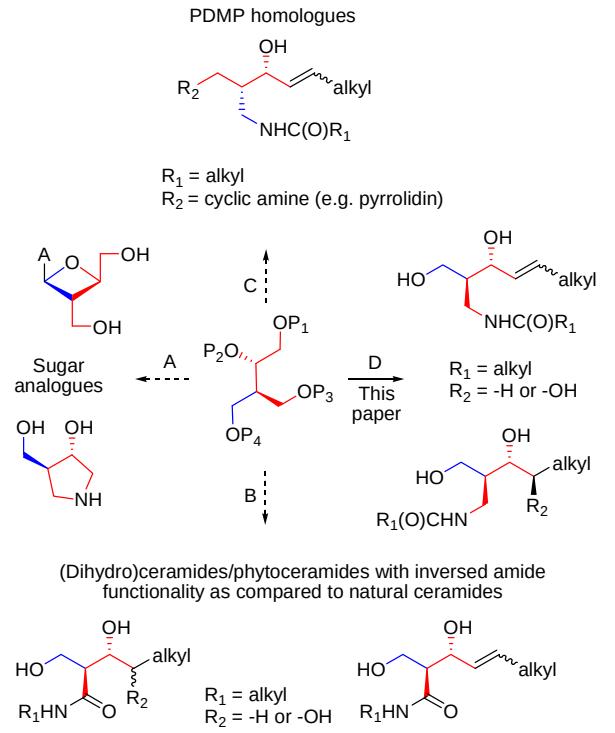


Figure 1. Synthetic potential of key intermediate (*S*)-3-(hydroxymethyl) butane-1,2,4-triol: **A**) (aza)sugar derivatives; **B**) ceramides and phytoceramides with an iversed amide functionality; **C**) PDMP homologues; **D**) N-(dihydro)homo(phyto)ceramides.

Here, we wish to demonstrate the usefulness of the (*S*)-3-(hydroxymethyl)butane-1,2,4-triol scaffold in preparing a novel class of homoceramide analogues (Figure 1; **D**), which contain an additional methylene group between the *N*-acyl chain and C2 (Figure 2; **2-4**). Interestingly, our procedure seemed also convenient for the synthesis of N-homophytoceramide (**5**), which can serve as key intermediate for the synthesis of α-galactosyl-N-homoceramide. This latter compound represents a homologue of α-galactosylceramide, a potentially useful agent for the treatment of autoimmune diseases.[6]

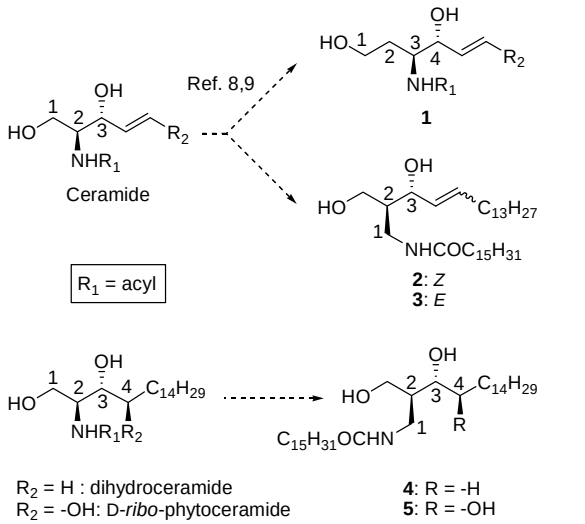


Figure 2. General stuctures of O_1-homoceramides (**1**) and N-(dihydro)homo(phyto)ceramides (**2-5**).

Homologation is a classical tool in medicinal chemistry to alter biological properties of endogenous compounds. Salbutamol, for instance, a widely[7] used bronchodilator with agonistic properties for β_2-receptors, consists of a 4-hydroxy-3-hydroxymethylphenyl moiety instead of the catechol ring, which is present in (nor)adrenaline.

Recently, our group reported an expedient route for the synthesis of D-*erythro*-O_1-homoceramides[8] (Figure 2; **1**). An alternative synthetic procedure for this class of non-natural ceramide analogues was later proposed by Ogino and coworkers.[9] The authors found that several representatives exhibited considerable apoptotic activities. Recently, Schmidt and coworkers[10] presented the synthesis of O_1-homosphingosine-phosphonate starting from D-galactose.

[3] Selected examples: (a) Ichikawa, E.; Yamamura, S.; Kato, K. *Tetrahedron Lett.* **1999**, *40*, 7285-7388. (b) Kikuchi, Y.; Kurata, H.; Shigeru, N.; Yamamura, S. *Tetrahedron Lett.* **1997**, *38*, 4795-4798. (c) Gumina, G.; Chu, C. K. *Org. Lett.* **2002**, *4*, 1147-1149. (d) Nishiyama, S.; Yamamura, S.; Kato, K.; Takita, T. *Tetrahedron Lett.* **1988**, *29*, 4743-4746.

[4] Abe, A.; Wild, S. R.; Lee, L.; Shayman, J. A. *Curr. Drug Metab.* **2001**, *2*, 331-338.

[5] (a) Radin, N. S. *Bioorg. Med. Chem.* **2003**, *11*, 2123-2142. (b) Reynolds, C. P.; Maurer, B. J.; Kolesnick, R. N. *Cancer Lett.* **2004**, *206*, 169-180.

[6] Representative reviews: (a) Van Kaer, L. *Nat. Immunol.* **2005**, *5*, 31-42. (b) Yamamura, T.; Miyamoto, K.; Illes, Z.; Pal, E.; Araki, M.; Miyake, S. *Curr. Top. Med. Chem.* **2004**, *4*, 561-567.

[7] Salbutamol is the representative for treatment of asthma and chronic obstructive pulmonary disease (COPD) in the WHO Essential Medicines Library (EMLib); Web site: http://mednet3.who.int/EMLib.

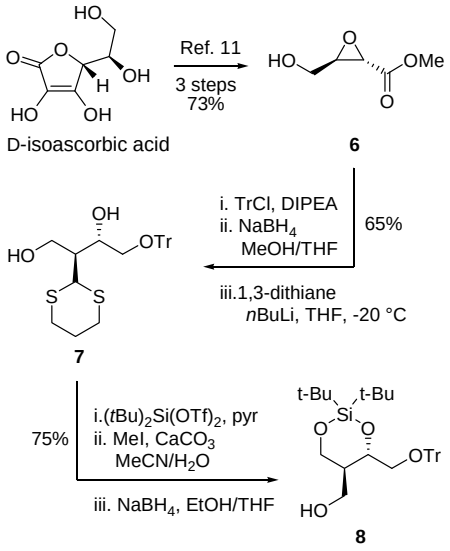
[8] De Jonghe, S.; Lamote, I.; Venkataraman, K.; Boldin, S. A.; Hillaert, U.; Rozenski, J.; Hendrix, C.; Busson, R.; De Keukeleire, D.; Van Calenbergh, S.; Futerman, A. H.; Herdewijn, P. *J. Org. Chem.* **2002**, *67*, 988-996.

[9] (a) Shikata, K.; Niiro, H.; Azuma, H.; Tachibana, T.; Ogino, K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 613-616. (b) Shikata, K.; Niiro, H.; Azuma, H.; Ogino, K.; Tachibana, T. *Bioorg. Med. Chem.* **2003**, *11*, 2723-2728.

[10] Tarnowski, A.; Retz, O.; Bar, T.; Schmidt, R. R. *Eur. J. Org. Chem.* **2005**, *6*, 1129-1141.

Epoxide synthon **6** (Scheme 1), prepared from D-isoascorbic acid as previously described,[11] provided the stereochemical and structural features required for our synthetic approach. Since epoxide opening is often hampered by regioselectivity issues involving the use of hazardous cyanide[1b] or additional synthetic steps implicated in allylic transformations[3b], we opted to use 1,3-dithiane[12] to introduce branching.

Scheme 1. Synthesis of key intermediate **8**.



Hence, tritylation followed by reduction of the ester and subsequent epoxide opening with 2-lithio-1,3-dithiane[13] produced intermediate 1,3-diol **7** with complete regioselectivity (47% yield in six steps from D-isoascorbic acid). Protection of 1,3-diol **7** with di-*tert*-butylsilyl ditriflate followed by dithiane deprotection with MeI under alkaline conditions and final reduction of the unmasked aldehyde with $NaBH_4$ gave access to **8** (75% from **7**, 36% from D-isoascorbic acid in 9 steps), which represents a unique intermediate from which each of the primary alcohols can selectively be addressed for further modification.

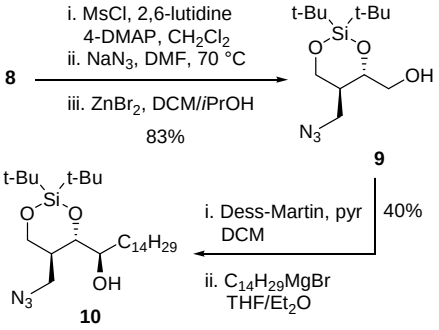
Access to D-*ribo*-N-homophytoceramide **5** is outlined in Schemes 2 and 3. Mesylation of intermediate **8** followed by azide introduction and trityl removal yielded alcohol **9** in good yield (83%). Subsequent periodinane oxidation and addition of tetradecylmagnesium chloride to the thus formed aldehyde furnished protected azido-N-homophytosphingosine **10** (40%) as a single diastereomeric form.

[11] (a) Dunigan, J.; Weigel, L. O. *J. Org. Chem.* **1991**, *56*, 6225-2557. (b) Ikunaka, M.; Matsumoto, J.; Fujima, Y.; Hirayama, Y. *Org. Process Res. & Dev. 1*, **2002**, *6*, 49. (c) Ziegler, F. E.; Belema, M. *J. Org. Chem.* **1994**, *59*, 7962.

[12] For a review on the role of 1,3-dithianes in natural product synthesis see: Yus, M.; Nájera, C.; Foubelo, F. *Tetrahedron* **2003**, *59*, 6147-6212.

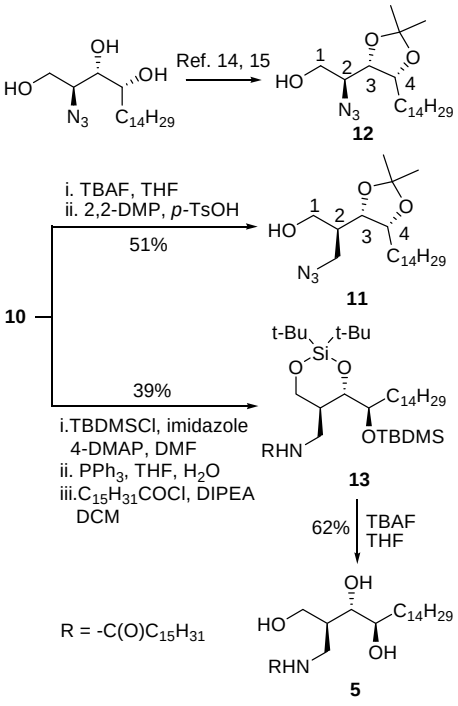
[13] Paquette, L. A.; Boulet, S. L. *Synthesis* **2002**, 888-894.

Scheme 2. Synthesis of azido intermediate **10**.



Assignment of the *erythro* configuration was achieved by converting intermediate **10** to the 3,4-isopropylidene protected triol **11** in a two steps sequence entailing silyl deprotection and dioxolane formation (Scheme 3; 51%) and subsequent comparison of ^1H NMR data with similarly protected natural D-*ribo*-azidophytosphingosine **12**.[14,15]

Scheme 3. Synthesis of D-*ribo*-N-homophytoceramide **5**.

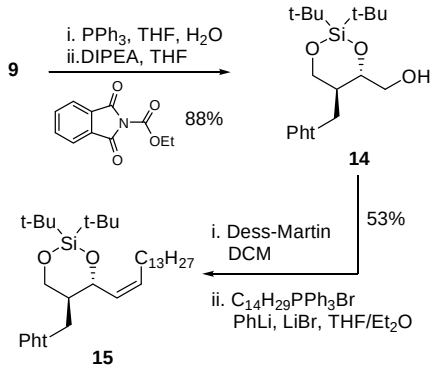


[14] (a) Compound **12** has been prepared according to literature procedures starting from commercially available D-*ribo*-phytosphingosine (ref. 15) (b) Both **11** ($^3J_{3,4}$ = 5.57 Hz) and **12** ($^3J_{3,4}$ = 5.38 Hz) exhibit a comparable vicinal coupling constant thereby indicating a cis-relationship of the ring substituents (standard sphingolipid numbering is used for clarity reasons).

[15] Schmidt, R. R.; Maier, T. *Carbohydr. Res.* **1998**, *174*, 169-179.

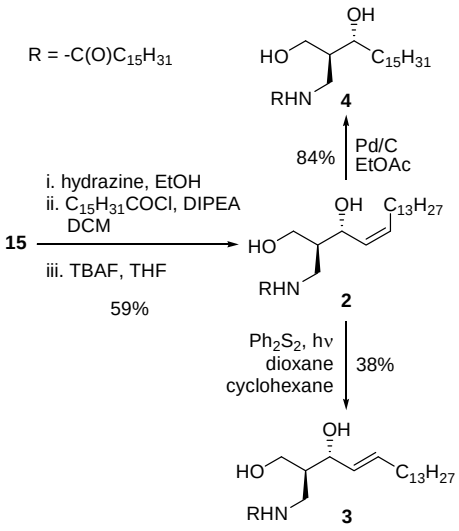
Azide reduction under Staudinger conditions following TBDMS protection of the secondary alcohol in **10** and subsequent acylation of the primary amine with palmitoyl chloride afforded silyl protected intermediate **13** (39%). Final desilylation with TBAF furnished D-*ribo*-N-homophytoceramide **5** (62%).

Scheme 4. Synthesis of *Z*-alkene intermediate **15**.



Since the presence of azides in Wittig olefination has led to controversial results,[16] we opted to transform the azide to a phthalimide in a two step sequence involving reduction of **9** under Staudinger conditions followed by phthalimide protection of the thus formed primary amine, thereby affording intermediate **14** in good yield (Scheme 4; 88%).

Scheme 5. Access to (dihydro)-N-homoceramides **2**-**4**.



Subsequent oxidation of the primary alcohol with Dess-Martin periodinane yielded the intermediate aldehyde. Although reaction conditions specifically addressed the *E*-isomer, Schlosser-Wittig olefination surprisingly only produced *Z*-isomer **15**. Hydrazine mediated phthalimide deprotection followed by acylation with palmitoyl chloride and silyl deprotection with TBAF furnished *Z*-N-homoceramide **2** (Scheme 5; 59%). Photo-induced double bond isomerisation in the presence of diphenyl disulfide as sensitizer produced, after two recrystallisations, isomerically pure *E*-N-homoceramide **3** (38%). Finally, hydrogenation of the *Z*-double bond in **2** gave access to dihydro-N-homoceramide **4** (84%).

In summary, we have reported an expedient route towards a versatile (*S*)-3-(hydroxymethyl)butane-1,2,4-triol scaffold starting from D-ascorbic acid, a common food preservative. The key transformation in this approach was the introduction of branching through a high yield and fully regioselective 2-lithio-1,3-dithiane epoxide opening. Based on this flexible synthon, we report the first synthesis of (dihydro)-N-homoceramides **2**-**4**. In addition, a fully stereoselective Grignard reaction gave access to D-*ribo*-N-homophytoceramide **5**, which will be utilised in a further study towards the elaboration of its α-galacosyl derivative.

Acknowledgment. We wish to thank S. Goormans for kindly providing a sample of compound **12**. SVC is indebted to the "Fonds voor Wetenschappelijk Onderzoek-Vlaanderen" for financial support ("krediet aan navorser").

Supporting Information Available. Full experimental details and copies of ^{1}H and ^{13}C spectra are available free of charge via the Internet at http://pubs.acs.org

[16] Selected examples: (a) Nugent, T. C.; Hudlicky, T. *J. Org. Chem.* **1998**, *63*, 510-520. (b) Timmer, M. S. M.; Verdoes, M.; Sliedregt, L. A. J. M.; van der Marel, G. A.; van Boom, J. H.; Overkleeft, H. S. *J. Org. Chem.* **2003**, *68*, 9406-9411.(c) Hudlicky, T.; Nugent, T. *J. Org. Chem.* **1994**, *59*, 7944-7946.